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10/595,619	05/01/2006	Heinz Von Der Kammer	2335.0160000/SRL/KPQ	3638

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,619	VON DER KAMMER ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-8,12 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-8,12 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment and Response, filed 7/23/09, has been entered. Claims 1-3, 9-11, 13-19 and 21-28 are cancelled; claims 4-8, 12 and 20 are amended and under current examination.

Election/Restrictions

Applicant's election without traverse of Group III (claims 4-8, 12, 19-23) in the reply filed on 12/19/08 is acknowledged.

Claims 1-3, 5-11, 13-18 and 24-28 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected groups, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/19/08.

Claim Objections

The objection to claim 12 is withdrawn in view of Applicants' amendment to the claim which incorporates non-elected claim 11.

Claims 6-7 are objected to under 37 CFR 1.75 as being a substantial duplicate of claim 4. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 6-7 do not further limit claim 4 because they recite phenotypes of the non-human animal. These phenotypes would be inherent in the animal, and therefore do not further limit the animal. Appropriate correction, such as incorporation of these limitations into independent claim 4, is suggested.

Claim Rejections - 35 USC § 101/112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-8, 12 and 20 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Applicants have now amended the claims to recite a genetically altered non-human animal comprising a non-native gene sequence coding for DAX-1, wherein the non-human animal is a fly or a mouse. Additional embodiments limit the phenotype of the animal. Further embodiments are directed to utilizing the animal to develop diagnostics and therapeutics to treat neurodegenerative diseases.

Applicants' Arguments. Applicants traverse the rejection and argue that claims as amended, now require that the claimed disease is Alzheimer's disease, and the claimed methods have at least the use of studying Alzheimer's disease, and the models are useful for studying modulation of the DAX-1 gene *in vivo*. See p. 5 of the Response.

Response to Arguments. These arguments are considered but are not found to be persuasive. The specification teaches that DAX-1 expression is found in human AD samples (p. 2, last ¶) but teaches that to date, no experiments have been described that demonstrate a relationship between the dyregulation of DAX-1 gene expression and the pathology of neurodegenerative disease, such as AD. See p. 5, last sentence and pages 12-13, bridging sentence. Thus, the specification teaches dysregulation of DAX-1 expression, and suggests a putative link between the up-

regulation of DAX-1 and diagnosis and treatment of neurodegenerative diseases, such as AD (see p. 13, 1st ¶, last sentence). However, at the time of filing, the skilled artisan would not have found any of the contemplated utilities as evidence of utility because neither the art, nor the specification, provide a correlation between the up-regulation/over-expression of DAX-1 and neurodegenerative diseases, such as AD. The specification provides, at best, a prophetic suggestion of DAX-1's role in AD, but there is no clear teaching in the specification with regard the actual function of DAX-1 in AD, other than the overexpression data. One of skill in the art could not rely upon the state of the art because as stated by the specification, there have been no experiments that demonstrated any relationship between dysregulation of DAX-1 gene expression and the pathology of neurodegenerative diseases, such as AD. The teachings of the art, at the time of filing, and the specification, provide no guidance with regard to the function of the protein encoded by DAX-1 with respect to any neurodegenerative disease. Thus, any correlation between the mutation of this particular gene and a particular disease cannot be determined. The specification provides, at best, a prophetic suggestion of DAX-1's role in AD. Thus, the function of the DAX-1 gene, or its encoded protein, is not known in the art, is not disclosed in the specification at the time of filing, the utility of the claimed invention is not apparent. It is further noted that the specification only teaches rescue of flies in DAX-1 coexpression assays. The specification provides no guidance for transgenic animals only expressing DAX-1.

Given that no specific correlation has been made between DAX-1 and AD, utilizing genetically altered, non-human animals comprising a gene sequence coding for DAX-1 as a model or to study Alzheimer's disease would not have an apparent utility. Additionally, utilizing the animals of the claimed invention to study modulation of the DAX-1 gene *in vivo* is not considered an apparent utility. In particular, a specific utility is that which is specific to the subject matter claimed. Studying gene function is a general utility that would be applicable to any

transgenic animal. MPEP §2107.01, which discusses specific utility, provides further support for this. The instant disclosure lacks a correlation between the DAX-1 gene and any particular disease is analogous to what is stated in the MPEP: "For example, indicating that a compound may be useful in treating unspecified disorders, or a compound that has "useful biological" properties, would not be sufficient to define a specific utility for the compound." Transgenic animals may not be capable of elucidating the function of a protein encoded by a gene, they may only provide a *clue* to the pathway of the transgenic gene. Note that it was scientifically well-known to introduce a transgene in to determine *in vivo* function; however, scientific utility is not the same as patentable or well-established utility. The MPEP and utility guidelines clearly set forth that a "well-established utility" must be specific, substantial, and credible. At the time of filing, a transgenic animal, such as that instantly claimed, wherein the DAX-1 gene has not been specifically characterized, would be used for further research, but further research does not rise to the level of a well-established utility because such a utility is not substantial, specific or credible.

The utilty guidelines specifically state that further research is not a "substantial utility":

> [T]he following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore do not define "substantial utilities":
>
> A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material involved.

In the instant case, further study of the animals would be required to determine how to use the genetically-altered animals as a model of disease, particularly because the instant specification fails to provide a specific correlation between DAX-1 overexpression and AD.

Under the utility guidelines set forth above, requirement for further research or experimentation renders the claimed invention as lacking in a specific or substantial utility. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real-world" context of use are not considered substantial utilities. The evidence of record has not provided any other utilities for the transgenic non-human animals encompassed by the claims that are substantial and specific. Finally, the use of the transgenic animals in determining function of the DAX-1 gene is not sufficient for utility because the relationship between the observed phenotypes and gene function do not necessarily correlate. Additional research would be required based on the present disclosure to determine if the phenotypes were related to DAX-1 gene function. Accordingly, the rejection is maintained.

Enablement

Claims 4-8, 12 and 20 stand rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 4-8, 12 and 20 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of

the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants' Arguments. Applicants argue that the claims have been amended to narrow the scope, with regard to mice or flies having a non-native gene sequence coding for DAX-1. Applicants argue that the claims are now directed to only AD and not neurodegenerative diseases in general. Applicants argue that one of skill in the art would be able to make and use the claimed invention when considering the specification in combination with the state of the art at the time of filing. See p. 6 of the Response.

Response to Arguments. These arguments are fully considered, but are not found to be persuasive. The specification provides no guidance for a genetically altered fly or mouse comprising a non-native gene sequence coding for DAX-1, other than the co-expression of DAX-1 with various other genes (see examples, pages 46-47). However, these rescue assays fail to provide a specific role or elucidation of function for DAX-1 in AD. The specification does not teach a transgenic fly with only the DAX-1 gene. In particular, the working examples fail to provide guidance to show that an animal that expresses DAX-1 would have a phenotype of 1) a predisposition to developing symptoms of Alzheimer's disease (claim 6); or 2) a reduced risk of developing symptoms similar to a AD. There is no guidance that simply expressing DAX-1 would result in the phenotypes that are encompassed by the claims. Additionally, the specification only describes experiments in Drosophila. Although the specification discusses the production of DAX-1 transgenic mice, there is no discussion of the phenotype of these mice.

The Examiner has provided guidance with regard to the unpredictability in the art with regard to production of a transgenic animal, with a particular phenotype. In particular, one of skill in the art, given the limited teachings provided by the specification, could not rely upon the state of the art of producing

transgenic animals, to predictably produce a transgenic fly or mouse comprising a non-native sequence coding for DAX-1, with a specific phenotype. See also, O'Kane, Kappell, Mullins, Cameron (all cited previously).

Applicants have now amended the claims to encompass transgenic mice. However, the specification fails to provide an enabling disclosure for the preparation of the claimed transgenic mice exhibiting an appropriate phenotype. Because the specification discloses no phenotype for the transgenic mice, undue experimentation would have been required for one of skill in the art to make and/or use the claimed invention. To this end, the specification does not provide guidance for any particular phenotype for the claimed transgenic mice, other than the anticipated expression of the transgene.

Note that the mere capability to perform gene transfer in a mouse is not enabling because a desired phenotype cannot be predictably achieved by simply introducing transgene constructs of the types recited in the claims. While gene transfer techniques are well developed for a number of species, and in particular, the mouse, methods for achieving the desired level of transgene expression in appropriate tissues are less well established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects [see Ryan *et al.*, **Sem. Neph.** 22:154-160, 2002] can dramatically influence the phenotype of the resultant transgenic animal. Ryan *et al.* state that methods such as pronuclear injection or gene targeting by homologous recombination are still limited by several unpredictabilities, including differences in transgene copy number and position of integration into the genome. Furthermore, Ryan *et al.* state "The location of integration can have dramatic effects on the expression of a transgene. Called the position effect, transcriptional regulatory

sequences at or near the insertion site can strongly influence your transgene, even impart a new set of instructions. " [See p. 155, 2nd column].

Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic animal depends upon the particular gene construct used, to an unpredictable extent. This is supported by Holschneider *et al.* [**Int J. Devl. Neuroscience** 18:615-618, 2000] who state that the, "knocking out or insertion of a single gene may result in no phenotypic change. This may be the case, in particular, if there exist gene redundancy mechanisms whose presence may prevent abnormal phenotypes from becoming masked. Conversely, single genes are often essential in a number of different behaviors and physiologic processes. Hence, ablation of an individual gene may prove so drastic as to be lethal, or so widespread as to create an amalgam of phenotypes whose interpretation becomes confounded by the interactions of the various new physiologic changes or behaviors." [See p. 615, col. 1-2]. Holschneider *et al.* discuss various factors that contribute to the resulting phenotype of transgenic mice, including compensatory systems which may be activated to mask the resulting phenotype, these compensatory changes may be due to the differential expression of another gene, which may be regulated by the downstream product of the ablated gene, as well as the variability in phenotypic characterization due to particular mouse strains [see p. 616, 1st column].

Given that specific phenotypic alterations cannot be predictably achieved by merely transferring a gene of interest into an animal, specific guidance must be provided to enable the instant invention. The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The claims cover the use of the claimed transgenic mice in methods of screening compounds, but the specification does not enable this use.

Accordingly, in view of the state of the art with regard to producing the sheer number of animals encompassed by the claims, the undeveloped and unpredictable state of the art, with regard to the generation of any non-mammalian transgenic

animal, or invertebrate, or even insect, the unpredictable state of the art with regard to producing a transgenic animal with a particular phenotype, the lack of working examples or guidance provided by the instant specification to overcome these art-recognized unpredictibilities, it would have required undue experimentation for one of skill in the art to make and use the claimed invention.

Written Description

The prior rejection of claims 4-8, 12 and 19-23 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicants' amendment to the claim, which no longer recite a fragment, derivative or variant of DAX-1.

Claim Rejections - 35 USC § 112

The prior rejection of claims 7-8 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicants' amendments to the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 6 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 remains unclear. In particular, the claim recites that the non-human animal has a reduced risk of developing symptoms *similar* to AD. The term *similar* is a relative term and therefore, it is unclear how similar a symptom to Alzheimer's disease must be in order to define the metes and bounds of the claim.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632